fracture, but is a protective factor for lower leg fracture, whereas high BMI is a risk factor for upper arm (humerus and elbow) fracture. When adjusted for BMD, low BMI remained a risk factor for hip fracture but was protective for osteoporotic fracture, tibia and fibula fracture, distal forearm fracture, and upper arm fracture. When adjusted for BMD, high BMI remained a risk factor for upper arm fracture but was also a risk factor for all osteoporotic fractures. The association between BMI and fracture risk is complex, differs across skeletal sites, and is modified by the interaction between BMI and BMD. At a population level, high BMI remains a protective factor for most sites of fragility fracture. The contribution of increasing population rates of obesity to apparent decreases in fracture rates should be explored. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: BMI; FRACTURE RISK; POPULATION STUDIES; POISSON REGRESSION MODEL; WOMEN; OBESITY

Introduction

Fractures are an important cause of morbidity in the population, especially in women. Hip fractures in particular are a major cause of pain, loss of function, and increased mortality, and are associated with very high costs to society.[1–3] Because fracture incidence increases with age, the burden from fracture is predicted to increase in the future due to an increase in the elderly population.[3–5]

In addition to low bone mineral density (BMD), many risk factors for fragility fractures have been identified.[2,6,7] Strong risk factors include a prior fragility fracture, a family history of fracture, exposure to glucocorticoids, and low body mass index (BMI).[8–11] Low BMI has been considered a risk factor for fracture, and obesity has been considered a protective factor for fracture,[11–13] but this association has recently been challenged.[14,15] Compston and colleagues[15] reported that obesity was not protective against fracture in postmenopausal women and, indeed, was associated with an increased risk of ankle and upper leg fractures. Similarly, Prieto-Alhambra and colleagues[16] concluded that obesity, though protective against hip and pelvis fracture, was associated with an increase in risk for proximal humerus fractures. In a recent review, Nielson and colleagues[17] stated that the importance of fractures occurring in the overweight and obese elderly may have been lost in the message that being underweight increases the risk of fracture.

The aim of this study was to investigate the association between BMI and future fracture risk at different skeletal sites in 25 international prospective cohorts comprising almost 400,000 women.

Subjects and Methods

Cohorts studied

We used baseline and follow-up data from 25 prospective cohorts, the majority of which were population based (20/25). Details of each of the cohorts are published elsewhere, but are summarized briefly below and in Tables 1, 2, and 3.

The Adult Health Study (AHS) at the Radiation Effects Research Foundation was established in 1958 to document the late health effects of radiation exposure among atomic bomb survivors in Hiroshima and Nagasaki, Japan. The original AHS cohort consisted of about 15,000 atomic bomb survivors and 5000 controls selected from residents in Hiroshima and Nagasaki using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. AHS subjects have been followed through biennial medical examinations since 1958.[18,19] In the Aberdeen Prospective Osteoporosis Screening Study from the UK (APOSS),[20] women were randomly selected from a community-based register and invited to participate in a population-based screening program for osteoporotic fracture risk. The Canadian Multicentre Osteoporosis study (CaMos) is an ongoing prospective age-stratified cohort of men and women ages 25 to 80+ randomly selected from regional residential telephone listings. The sampling frame was a 50-km radius around nine study centers in seven provinces, and participants are representative of 41% of the population of Canada.[21] The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study from Dubbo, Australia.[22] The Ecografía Osea en Atención Primaria (ECOSAP) study was a referral population recruited in 58 primary care center throughout Spain, regardless of the reason for consultation.[23] The Norfolk cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk) comprises men and women aged 40 to 79 years who were resident in Norfolk, UK, at the time of recruitment and were recruited from general practice listings.[24] The Epidemiologie de l'osteoporose (EPIDOS) study comprises a population-based cohort from five French centers (Amiens, Lyon, Montpellier, Paris, and Toulouse)[25]: women were recruited through mailings using large population-based listings such as voter registration rolls. The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centers in 19 European countries.[26] Equal numbers of men and women were drawn in each center within six 5-year age bands (50–74 and 75+ years). BMD was measured in 13 centers. This sample provided the framework for the European Prospective Osteoporosis Study (EPOS), in which repeated assessment was undertaken in 29 of the centers.[27,28] The Gothenburg I subjects were drawn randomly from the population register in Gothenburg, Sweden, by the date of birth to provide cohorts aged 70, 76, 79, and 85 years at the time of investigation.[29] The Gothenburg II study comprised a randomly drawn population that attended for mammography screening.[30] The Geelong Osteoporosis Study (GOS) is an age-stratified sample of women drawn randomly from the electoral roll of Geelong and surrounding districts in south eastern Australia.[31] The Manitoba cohort is a referral population of all women attending for BMD measurements in the Province of Manitoba, Canada, where health services are provided to residents through a single public healthcare system.[32] The Miyama study is a population-based cohort drawn from inhabitants born in Miyama, Japan, between 1910 and 1949.[33] Of 1543 inhabitants, an age-stratified sample of 400 men and women was drawn by birth decade. The MsOS study is a cohort study on osteoporosis in a convenience sample of ambulant Asian women recruited from the community in Hong Kong.[34] The Os des Femmes de Lyon (OFELY) cohort comprised an age-stratified female cohort randomly selected from the regional section of a large health insurance company (Mutuelle Generale d'Education Nationale, Lyon, France).[35] The Osteoporosis and Ultrasound Study (OPUS) comprises five age-stratified population-based female cohorts drawn from different European centers (Sheffield and Aberdeen in the UK; Berlin and Kiel in Germany; and Paris in France).[36] The Kuopio osteoporosis

Table 1. Cohorts Studied

Cohort	Year for baseline	Bone densitometry	Fracture report
AHS	1958 (BMD: 1994)	DXA FN, Hologic QDR 2000	Spinal radiographs and self-report
APOSS	1990–1994	DXA left FN, Norland (Cooper Surgical)	Self-report, computer reports from radiologists, hospital record, primary care physicians' record
CaMos	1996–1997	DXA FN, Hologic QDR and Lunar DPX Alpha phantom-calibrated across centers and machines	Self-report. Radiographic or medical report verification of incident fractures was obtained when information was available.
DOES	1989	DXA FN, GE-Lunar, DPX and Prodigy	Radiologists' report
ECOSAP[a]	2000–2001	QUS right calcaneus, Sahara (Hologic)	Self-report, confirmed by investigator by X-ray or radiological or surgical reports
EPIC-Norfolk[b]	1997–2000	–	Hospital record linkage
EPIDOS	1992–1993	DXA FN, Lunar DPX	Self-report, family, or physician
EVOS/EPOS	1989	DXA FN, cross-calibrated using European Spine Phantom	Self-reported fractures were confirmed where possible by radiograph, attending physicians or subject interview
GBG I	1985–1993	Dual photon absorptiometry right heel	Radiology departments servicing the region
GBG II[a]	1992–1997	Distal forearm, Osteometer DTX-200	Radiology departments servicing the region
GOS	1994–1997	DXA FN, Lunar DPX-L	Radiographically confirmed from hospital records
Manitoba[a]	1990–2007	DXA FN, Lunar DPX or Lunar prodigy	Ascertained using ICD codes, where two or more hospitals or physicians ICD fracture codes had to be present to confirm a fracture. Site-specific orthopedic intervention codes for hip and forearm fractures.
Miyama	1989–1990	DXA FN, Lunar DPX	Self-report, confirmed by X-ray
MsOs HK[a]	2001	DXA FN, Hologic QDR-4, 500-W	Self-report, confirmed by X-ray or medical record
OFELY	1992–1993	DXA FN, Hologic QDR 2000	Radiography, X-rays, surgical reports
OPUS	1999–2001	DXA FN, Hologic QDR 4500 or Lunar Expert	Spinal radiograph; verification of non-vertebral incident fractures when information was available.
OSTPRE	1989	DXA FN, Lunar DPX	Self-report
PERF	1977–1997	DXA FN, Hologic QDR-2000	Spinal radiographs and self-report
Rochester	1980	DXA FN, Hologic QDR 2000 and dual-photon absorptiometry cross-calibrated to DXA	Self-report combined with review of the in-patient and outpatient medical records of all local care providers
Rotterdam	1990–1993	DXA FN, Lunar DPX-L	Automatic link with general practitioner computer systems and hospital admission data. Validated by two independent research physicians.
SEMOF	1997–1999	DXA FN, Hologic QDR 4500	Questionnaire and confirmed from medical records
Sheffield	1993–1999	DXA FN, Hologic QDR 4500	Self-report at home visits
SOF[a]	1986–1988 (BMD: 1990–1991)	DXA FN, Hologic QDR 1000	Telephone or correspondence and confirmed from X-ray reports
THIN	1995–2004	–	General practitioners' records

(*Continued*)

Table 1. (*Continued*)

Cohort	Year for baseline	Bone densitometry	Fracture report
WHI[a]	1990	DXA FN, Hologic 2000	Hip fractures by medical records and adjudicated at a central facility. Other fractures were adjudicated locally (clinical trials) and by self report (observational study for patients without BMD).

AHS = Adult Health Study; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; FN = femoral neck; QDR = quantitative digital radiography; *APOSS* = Aberdeen Prospective Osteoporosis Screening Study; *CaMos* = Canadian Multicentre Osteoporosis study; *DOES* = Dubbo Osteoporosis Epidemiology Study; ECOSAP = Ecografía Osea en Atención Primaria; QUS = quantitative ultrasound; EPIC-Norfolk = Norfolk cohort of the European Prospective Investigation into Cancer; EPIDOS = Epidemiologie de l'osteoporose; EVOS = European Vertebral Osteoporosis Study; EPOS = European Prospective Osteoporosis Study; GBG I = Gothenburg I; GBG II = Gothenburg II; GOS = Geelong Osteoporosis Study; Manitoba = Province of Manitoba, Canada; ICD = International Classification of Diseases; Miyama = Miyama, Japan; MsOs HK = osteoporosis in Asian women in Hong Kong; OFELY = Os des Femmes de Lyon; OPUS = Osteoporosis and Ultrasound Study; OSTPRE = osteoporosis risk factor and prevention, Kuopio, Finland; PERF = Prospective Epidemiological Risk Factors; Rochester = two random population samples of women, Minnesota, USA; Rotterdam = ongoing study in Ommoord district, Rotterdam, the Netherlands; SEMOF = Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk; Sheffield = women ≥75 in Sheffield, UK; THIN = The Health Improvement Network; WHI = Women's Health Initiative.

[a]Denotes that the cohort was not population-based.

[b]EPIC Norfolk collected QUS data on approximately 15,000 men and women between 1997 and 2000; fractures were ascertained by hospital record linkage.

risk factor and prevention (OSTPRE) study in Finland comprised a postal inquiry sent to all 14,220 women who were residents of Kuopio province.[37] The Prospective Epidemiological Risk Factors (PERF) study was a population-based cohort in Copenhagen, Denmark.[38] The survey invited women to participate in screening for various placebo-controlled clinical trials and epidemiological studies in Copenhagen. The Rochester cohort was recruited from two random population samples of women from Minnesota, USA, stratified by decade of age.[39,40] The Rotterdam Study is an ongoing prospective cohort study that aimed to examine and follow all residents aged 55 years and older living in Ommoord, a district of Rotterdam, the Netherlands.[41–43] The Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk (SEMOF) study is a prospective multicenter study (10 centers in Switzerland).[44] Women were randomly selected from an address register. The Sheffield cohort comprised women aged 75 years or more selected randomly from the population of Sheffield, UK, and surrounding districts, identified from general practitioner listings. The women willing to participate and meeting inclusion criteria were randomly allocated to treatment with placebo or the bisphosphonate, clodronate, to study its effects on fracture risk. The subjects for this study comprised 2171 women allocated to treatment with placebo only.[45,46] The Study of Osteoporotic Fractures (SOF) is a multicenter cohort study of risk factors for osteoporosis and fracture.[47] Participants were ambulatory white women selected by convenience and recruited at four clinical centers from the United States (Baltimore, MD; Minneapolis, MN; Pittsburgh, PA; and Portland, OR, USA). The Health Improvement Network (THIN) research database was derived from computerized records of a sample of general practitioners in the UK, similar to the General Practice Research Database.[48] The study population comprised all women aged 50 years or more. The Women's Health Initiative (WHI) study comprises three overlapping randomized controlled studies and an observational study in a convenience sample of postmenopausal women.[49,50] The trials comprised dietary modification (low-fat diet) ($n = 48{,}836$), hormone replacement therapy (HRT) in women with or without a uterus ($n = 27{,}347$), and supplementation with calcium and vitamin D ($n = 36{,}282$). The total sample size was 161,808. For this analysis women taking bone active medication (HRT, bisphosphonates, and calcitonin) were excluded, leaving a sample size of 81,377.

Measurements

Height and weight were measured using standard techniques in all cohorts. BMI was calculated as weight in kilograms divided by height squared in meters and used as a continuous variable or categorized according to the WHO criteria[51]: underweight (BMI < 18.5 kg/m^2); normal (18.5–24.9 kg/m^2); overweight (25.0–29.9 kg/m^2); obese I (30.0–34.9 kg/m^2); and obese II (≥35.0 kg/m^2). BMD was assessed in 27% of the women using several different techniques summarized in Table 1 and converted to standardized cohort-specific *Z*-scores. The proportion of women with BMD measurement varied by cohorts from 0% to 100% (Table 2).

For fracture outcomes, we used information on fractures only at sites considered to be associated with osteoporosis[52]; ie, fractures of the spine, coccyx, ribs, pelvis, humerus, forearm, elbow, hip, other femoral, tibia and fibula, clavicle, scapula, and sternum. Fractures of the skull, face, hands and fingers, feet and toes, ankle, and patella were excluded. In addition to "osteoporotic fractures," incident hip, distal forearm, lower leg (tibia and/or fibula), and upper arm (humerus and/or elbow) were considered separately.

Statistical methods

Correlation tests between BMI and other variables used nonparametric Pitman's permutation test; Pearson correlation coefficients were also calculated.

The association between BMI and the risk of fracture was examined using an extension of the Poisson regression model[53] in each cohort. The observation period of each participant was divided in intervals of 1 month. The first fracture per person was counted for each relevant outcome. Covariates included current age and time since start of follow-up, and analyses were performed with and without adjustment for BMD. Interactions between BMD and BMI were also studied. The β-coefficients from each cohort were weighted according to the variance, and then

Table 2. Details of Cohorts Studied

Cohort[a]	Subjects (*n*)	Length of follow-up (years), mean (maximum)	Age (years), mean (range)	BMI (kg/m^2) mean (SD)	BMD (*n*)[b]
AHS	1,810	3.8 (6.8)	66 (47–95)	23.1 (3.6)	1,797
APOSS	5,110	7.0 (12.3)	48 (44–56)	25.5 (4.6)	5,102
CaMos	6,315	6.0 (8.6)	63 (25–103)	26.9 (5.2)	5,719
DOES	1,270	7.8 (13.6)	71 (57–94)	25.4 (4.6)	1,259
ECOSAP	5,128	2.9 (4.5)	72 (65-100)	29.2 (4.7)	–
EPIC-Norfolk	8,856	5.4 (6.9)	62 (42–81)	26.6 (4.4)	–
EPIDOS	7,593	3.4 (5.0)	80 (70-100)	25.4 (4.2)	7,560
EVOS/EPOS	9,013	3.0 (5.9)	64 (41–93)	27.2 (4.6)	2,761
GBG I	1,158	7.9 (16.3)	79 (69–85)	25.3 (4.2)	947
GBG II	7,065	12.4 (16.2)	59 (21–89)	24.6 (3.6)	7,056
GOS	1,863	6.3 (10.9)	63 (35–95)	26.8 (5.3)	1,805
Manitoba	43,860	5.3 (18.4)	62 (40–102)	26.6 (5.4)	43,186
Miyama	400	8.6 (13.0)	59 (40–79)	22.1 (2.8)	400
MsOs HK	2,000	3.5 (5.3)	73 (65–98)	23.9 (3.5)	2,000
OFELY	668	10.9 (14.2)	62 (50–89)	24.0 (3.5)	663
OPUS	2,881	6.0 (8.2)	61 (20–81)	26.3 (4.6)	2,836
OSTPRE	3,058	10.0 (10.0)	52 (47–57)	26.1 (4.3)	1,743
PERF	5,433	7.2 (24.0)	63 (44–81)	25.5 (3.9)	2,305
Rochester	655	8.1 (19.0)	58 (21–94)	25.5 (4.9)	650
Rotterdam	4,068	5.9 (9.4)	70 (55–99)	26.7 (4.1)	3,325
SEMOF	7,062	2.8 (4.9)	75 (70–91)	25.9 (4.3)	908
Sheffield	2,170	3.8 (5.8)	80 (74–96)	26.7 (4.5)	2,150
SOF	9,704	11.9 (20.6)	72 (65–99)	26.4 (4.6)	7,963
THIN	180,093	4.7 (13.9)	60 (50–105)	26.0 (5.1)	–
WHI	81,377	7.4 (11.2)	64 (49–79)	28.6 (6.2)	6,132
Totals	398,610	5.7 (24.0)	63 (20–105)	26.6 (5.4)	108,267

BMI = body mass index; BMD = bone mineral density.

[a]The cohort abbreviations are defined in detail in the Cohorts studied section of Subjects and Methods, and are defined in brief in the footnotes for Table 1.

[b]Subjects with BMD data available.

merged to determine the weighted mean of the coefficient and its SD. The associations between BMI and risk of fracture were described as the hazard ratio (HR) for fracture per 1-unit change in BMI together with 95% confidence intervals (CIs).

Heterogeneity between cohorts was tested by means of the I^2 statistic.[54] Heterogeneity was found for the osteoporotic fracture outcome ($I^2 = 75\%$; 95% CI, 63% to 83%) and the hip fracture outcome ($I^2 = 86\%$; 95% CI, 81% to 90%). When the interaction between BMI and current age was included, there was no significant heterogeneity between cohorts for BMI ($I^2 = 14\%$; 95% CI, 0% to 48%) for the outcome of osteoporotic fracture. For the outcome of hip fracture there was a moderate heterogeneity between cohorts for BMI ($I^2 = 61\%$; 95% CI, 39% to 75%). Because we had a moderate heterogeneity for the outcome of hip fracture even when including an interaction with age, we performed both a fixed and a random effect model when merging the result from the different cohorts. Overall the weighted β-coefficient describing the association between BMI and the outcome of osteoporotic fracture was −0.0215 when using a fixed-effect model and −0.0210 when using a random effect model (with a SD describing the variance between cohorts of 0.013), resulting in the same HR per 1-unit of 0.98. When describing the association between BMI and the outcome of hip fracture the β-coefficient was −0.0740 when using a fixed-effect model and −0.0719 when using a random effect model (with a SD of 0.014) resulting in the same HR per 1-unit of 0.93. Because the estimates were so similar, we used the fixed-effect model to present the results.

In order to study the association between BMI and fracture risk in more detail, a spline Poisson regression model was fitted using cohort specific knots at the 10th, 50th, and 90th percentiles of BMI, as recommended by Harrell.[55] The splines were second order functions between the breakpoints and linear functions at the tails, resulting in a smooth curve. When the comparisons between two points at the curve was done, a piecewise linear model with knot at BMI = 25 kg/m^2 were used to study the relationship between BMI and the risk of fracture.

In sensitivity analyses, we repeated the calculations (1) in those cohorts that were population-based (see Table 1); (2) in cohorts without excluding women that received treatments for osteoporosis; and (3) using a random-effect rather than a fixed-effect model.

Results

The cohorts comprised 398,610 women aged 20 to 105 years with an average age of 63 years, who were followed for approximately 2.26 million person-years (Tables 2 and 3). During an average follow-up of 5.7 years 30,280 osteoporotic fractures were documented, of which 6457 were at the hip (Table 3). The mean BMI was 26.6 kg/m^2 and approximately one-half of the

Table 3. Details of Incident Fractures by Cohort

Cohort[a]	Person-years	Incident fracture				
		Osteoporotic	Hip	Distal forearm	Tibia/fibula	Humerus/elbow
AHS	6,928	78	25	32	–	14
APOSS	34,588	236	7	113	–	47
CaMos	38,016	618	90	220	18	109
DOES	9,892	339	94	100	25	48
ECOSAP	14,811	282	52	108	–	49
EPIC-Norfolk	47,973	172	82	73	–	–
EPIDOS	25,714	1,056	311	312	–	237
EVOS/EPOS	20,945	520	30	153	36	43
GBG I	9,191	255	198	–	–	–
GBG II	87,577	887	116	443	31	98
GOS	7,315	143	32	34	9	15
Manitoba	232,076	2,855	536	1,070	–	770
Miyama	3,423	51	7	11	1	5
MsOs HK	6,975	96	21	43	–	8
OFELY	7,290	132	20	50	1	17
OPUS	12,019	113	13	68	–	28
OSTPRE	30,568	259	8	192	–	24
PERF	38,991	561	58	353	–	78
Rochester	5,318	219	42	39	16	20
Rotterdam	23,977	550	156	221	37	84
SEMOF	19,639	534	80	184	20	104
Sheffield	8,235	292	91	106	14	37
SOF	115,810	3,211	1,269	967	159	735
THIN	852,566	8,343	1,953	–	–	–
WHI	596,434	8,478	1,166	3,318	1,553	1,385
Totals	2,256,271	30,280	6,457	8,210	1,920	3,955
Age at fracture (years), mean (SD)		72.7 (10.4)	79.5 (8.8)	71.0 (9.6)	69.6 (8.5)	73.6 (9.7)

– = site of fracture not given.

[a]The cohort abbreviations are defined in detail in the Cohorts studied section of Subjects and Methods, and are defined in brief in the footnotes for Table 1.

women were overweight or obese (56%), with 22.1% being obese (Table 4). Approximately 7700 women (1.9%) were underweight. There was a weak but significant negative correlation between age and BMI ($p < 0.001$; $r = -0.01$; 95% CI, –0.01 to –0.01). For example, in women aged 55 to 59 years, 1.3% of women were underweight and the proportion increased progressively with age, so that 5.8% of women aged 85 to 89 years were underweight. Conversely, the prevalence of obesity decreased with age from 25.3% in the age group 55 to 59 years to 10.9% between the ages of 85 and 89 years. There was a significant positive correlation between BMI and BMD ($p < 0.001$; $r = 0.33$; 95% CI, 0.32–0.33). In underweight women, the mean BMD femoral neck *Z*-score was –0.89 and for the obese II category it was 0.67 (Table 4).

BMI and risk of fracture

A total of 30,280 osteoporotic fractures were reported during follow-up (Table 3). A minority (19%) of all osteoporotic fractures occurred in obese women (Table 5) and the observed number was lower than expected (5798 versus 6691, respectively) if BMI was assumed to exert no influence on fracture risk. Thus obesity was a protective factor for osteoporotic fractures as a whole. Similar results were found when hip fracture or distal forearm

Table 4. Baseline Characteristics by BMI Category

	Underweight (BMI <18.5)	Normal (BMI 18.5–24.9)	Overweight (BMI 25.0–29.9)	Obese I (BMI 30.0–34.9)	Obese II (BMI ≥35.0)
Subjects (*n*)	7,699	166,087	136,873	58,919	29,032
Age (years)	65.7 (14.0)	62.2 (11.6)	63.6 (10.7)	63.2 (10.1)	61.2 (9.3)
BMI (kg/m^2)	17.2 (1.3)	22.5 (1.6)	27.2 (1.4)	32.0 (1.4)	39.3 (4.5)
Femoral neck BMD (*Z*-score)	–0.89 (0.97)	–0.25 (0.93)	0.12 (0.94)	0.41 (0.96)	0.67 (1.0)
Subjects with BMD values (*n*)	2,309	46,796	37,741	15,051	6,370

Values are mean (SD).

BMI = body mass index (kg/m^2); BMD = bone mineral density.

Table 5. Number of Fractures According to Fracture Outcome and Category of Baseline BMI

	BMI categories[a]					Obese versus non-obese		
Fracture outcome	Underweight (1.9%)	Normal (41.7%)	Overweight (34.3%)	Obese I (14.8%)	Obese II (7.3%)	HR	95% CI	*p*
Osteoporotic	806 (575)	13,293 (12,627)	10,383 (10,386)	4119 (4481)	1679 (2210)	0.85	0.82–0.88	<0.001
Hip	320 (123)	3257 (2693)	2062 (2215)	628 (956)	190 (471)	0.63	0.59–0.68	<0.001
Distal forearm	126 (150)	3424 (3424)	2990 (2816)	1202 (1215)	468 (599)	0.81	0.76–0.86	<0.001
Tibia/fibula	10 (36)	608 (801)	704 (659)	361 (284)	237 (140)	1.04	0.94–1.14	>0.30
Humerus/elbow	76 (75)	1452 (1649)	1399 (1357)	694 (585)	334 (289)	1.21	1.11–1.31	<0.001

Values are the number of fractures in each BMI category and in parentheses are the expected number of fractures according to the percentage of women in each BMI category.

BMI = body mass index; HR = hazard ratio; CI = confidence interval.

[a]BMI categories (kg/m^2): Underweight, BMI <18.5; Normal, BMI 18.5–24.9; Overweight, BMI 25.0–29.9; Obese I, BMI 30.0–34.9; Obese II, BMI ≥35.0. Percentages are the proportion of women in each BMI category.

fractures were considered individually (Table 5). In contrast, the observed incidence of lower leg fractures was not reduced, and the risk of upper arm fractures was higher than expected in obese women.

When BMI was used as a continuous variable, there was a significant association between BMI and fracture risk ($p < 0.001$). In the case of all osteoporotic fractures, the HR per unit increase of BMI was 0.98 (95% CI, 0.98–0.98) and for hip fracture it was 0.93 (95% CI, 0.92–0.94). The HR was not, however, uniform across BMI; low BMI was associated with a greater risk than would be predicted from a uniform HR and, conversely, a high BMI contributed less to fracture prevention than expected. Thus, when studying the relationship in more detail with spline functions, the function was steeper below a BMI of 25 kg/m^2 than above this value (Fig. 1). When a woman with a BMI of 15 kg/m^2 was compared with a woman with a BMI of 25 kg/m^2 using piecewise linear functions, the HR was 1.5 (95% CI, 1.4–1.6) for osteoporotic fracture and 2.9 (95% CI, 2.6–3.3) for hip fracture (Table 6). By contrast, if a woman with a BMI of 25 kg/m^2 was compared to one with a BMI of 35 kg/m^2, the HR was 0.9 (95% CI: 0.9–0.9) for osteoporotic fracture and 0.7 (95% CI = 0.6–0.8) for hip fracture.

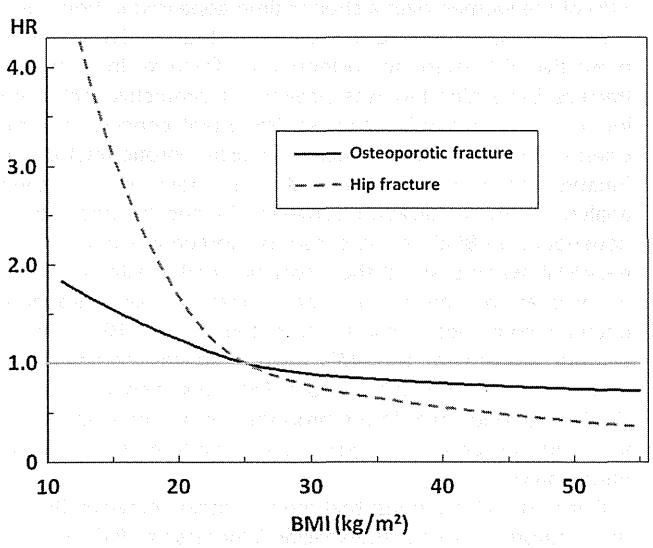

Fig. 1. Relationship between BMI and risk of fracture (HR versus BMI 25 kg/m^2) for osteoporotic fracture (solid line) and hip fracture (dashed line), adjusted for age and time since baseline. BMI = body mass index; HR = hazard ratio.

The use of BMI as a continuous variable also confirmed the different patterns between fracture sites. In the case of upper arm fractures, a BMI of 35 kg/m^2 conferred a significantly higher risk than a BMI of 25 kg/m^2, whereas a BMI of 15 kg/m^2 had a similar risk to that at 25 kg/m^2 (Table 6). The lower BMI was associated with a significant reduction in lower leg fractures, whereas the risk was similar at 25 and 35 kg/m^2 (Table 6).

Adjustment for BMD

When the association between BMI and hip fracture risk was adjusted for BMD, the association was weaker than in the absence of BMD but was still significantly negative. The HR was 0.99 per 1 kg/m^2 increase (95% CI, 0.98–0.99; $p = 0.0014$). When the relationship was examined with spline functions, the relationship was much flatter with BMD adjustment (Fig. 2) than without (Fig. 1). Not withstanding, the risk of hip fracture with low BMI was greater than the protective effect of a high BMI. Thus, a BMI of 15 kg/m^2 had an HR of 1.4 (95% CI, 1.2–1.7) compared to a BMI of 25 kg/m^2 (Table 6), but a BMI of 35 kg/m^2 conferred no greater hip protection than a BMI of 25 kg/m^2 (HR = 1.0; 95% CI, 0.9–1.2).

Interestingly, the association between BMI and osteoporotic fracture risk was weaker but inverted when adjusted for BMD, so that a higher BMI was now associated with a small but significant increase in fracture risk (HR per 1-unit increase in BMI = 1.01; 95% CI, 1.01–1.02; $p < 0.001$). For example, the HR for all osteoporotic fracture was 1.16 (95% CI, 1.09–1.23) when comparing a BMI of 35 kg/m^2 with a BMI of 25 kg/m^2; at a BMI of 15 kg/m^2, the risk was reduced. Thus, for all osteoporotic fractures a higher BMI was, if anything, a modest albeit significant risk factor following adjustment for BMD. A similar pattern was observed for distal forearm fractures. The association of high BMI with increased fracture risk following adjustment for BMD was most marked for upper arm fractures (Table 6). For lower leg fractures, fracture risk was increased and decreased at high and low BMIs, respectively, compared to 25 kg/m^2 (Table 6).

Table 6. HRs for Fracture and 95% CIs Comparing a BMI of 25 kg/m^2 With BMIs of 15 kg/m^2 and 35 kg/m^2, Respectively, According to Different Fracture Outcomes

	Not adjusted for BMD		Adjusted for BMD	
Fracture outcome	BMI 15 versus 25	BMI 35 versus 25	BMI 15 versus 25	BMI 35 versus 25
Osteoporotic	1.54 (1.44–1.64)	0.87 (0.85–0.90)	0.89 (0.80–0.99)	1.16 (1.09–1.23)
Hip	2.88 (2.56–3.25)	0.68 (0.62–0.75)	1.41 (1.16–1.72)	0.99 (0.86–1.15)
Distal forearm	1.05 (0.91–1.20)	0.76 (0.71–0.81)	0.72 (0.60–0.86)	0.97 (0.87–1.07)
Tibia/fibula	0.64 (0.45–0.89)	1.03 (0.94–1.14)	0.34 (0.16–0.74)	1.14 (0.87–1.49)
Humerus/elbow	1.13 (0.92–1.37)	1.18 (1.04–1.27)	0.70 (0.54–0.90)	1.60 (1.42–1.80)

Values are HR (95% CI), adjusted for age and time since baseline.
HR = hazard ratio; CI = confidence interval; BMI = body mass index; BMD = bone mineral density.

Interactions with BMI

There was a significant interaction between age and BMI for osteoporotic fracture ($p < 0.001$). This age interaction was significant both below and above a BMI of 25 kg/m^2 ($p = 0.042$ and $p < 0.001$, respectively). Thus, when BMI was set at 15 kg/m^2 and compared with a BMI of 25 kg/m^2 using piecewise linear functions, the HR was 1.4 at the age of 50 years and 1.7 at the age of 80 years, suggesting that low BMI was a stronger risk factor for osteoporotic fractures in elderly women. The same age-BMI interaction was true for BMI greater than 25 kg/m^2, in that high BMI was a stronger protective factor for elderly women. A significant interaction between age and BMI was seen for hip fracture below a BMI of 25 kg/m^2 ($p < 0.001$), but not for BMI above 25 kg/m^2 ($p = 0.058$). Thus, when BMI, set at 15 kg/m^2, was compared with a BMI of 25 kg/m^2 using piecewise linear functions, the HR was 9.2 at the age of 50 years and 3.1 at the age of 80 years, indicating that low BMI was a stronger risk factor for hip fracture in younger women than in elderly women.

Because there was a significant correlation between BMD and BMI, and BMD affected the relationship between BMI and the risk of fracture, the interaction between BMI and BMD was investigated with both linear and cubic models. No such interactions were found, indicating that the correlation between BMI and fracture risk did not change for different values of BMD. There were also no significant interactions between BMI and time since baseline; ie, the predictive value of BMI did not change with time ($p > 0.20$ for both osteoporotic and hip fracture outcomes).

When women allocated to treatments for osteoporosis in the WHI cohort were included, the results were similar. So, too, were the results when the analysis was confined to population-based cohorts.

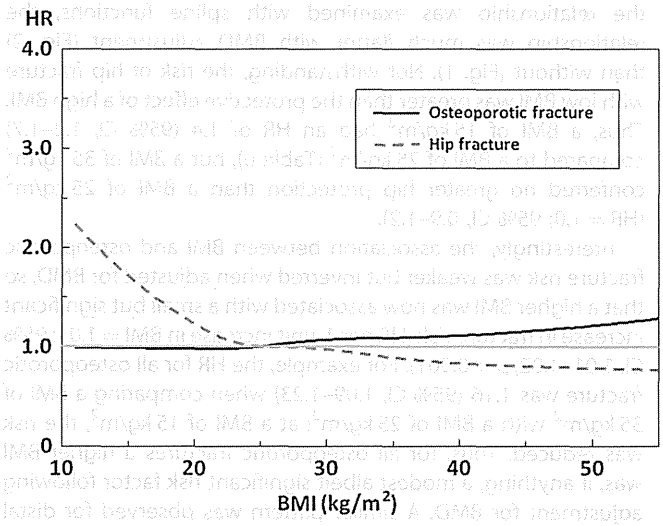

Fig. 2. Relationship between BMI and risk of fracture (HR versus BMI 25 kg/m^2) for osteoporotic fracture (solid line) and hip fracture (dashed line), adjusted for age, time since baseline, and BMD. BMI = body mass index; HR = hazard ratio; BMD = bone mineral density.

Discussion

The principal finding of the present meta-analysis of predominantly prospective population-based cohorts of women is the significant association between BMI at baseline and future osteoporotic fracture, in that a low BMI was a significant risk factor for all osteoporotic fractures, including hip and forearm fractures. These finding are very consistent with an earlier but smaller meta-analysis,[11] though it should be acknowledged that 11% of the women over a shorter time appeared in both meta-analyses. As previously reported in that study, a high BMI was a protective risk factor for osteoporotic fracture, including hip fracture, but a high BMI was weaker as a protective factor than low BMI was as a risk factor. An important conclusion is that obesity itself is not a risk factor for osteoporotic fracture, hip fracture, or forearm fracture. As also seen in the earlier analysis,[11] the association between BMI and fracture risk was dependent on BMD. In the subset of women in whom femoral neck BMD was measured, the association of BMI with hip fracture risk was attenuated and was not evident for all osteoporotic fractures combined. It should be noted that the HRs with and without adjustment for BMD are not strictly comparable; a minority of women (27%) had a BMD test and there was a significant cohort bias in the proportion of women with a BMD test. With this caveat, the results are consistent with the earlier meta-analysis.

Our results also suggest that the association between BMI and risk of future fracture is site-specific. Whereas low BMI was a risk factor for all osteoporotic fractures, a low BMI was a protective factor for lower leg fracture. In this regard, several of the cohorts did not adequately distinguish fractures of the lower leg that are associated with low BMD (eg, proximal tibial fractures) from ankle fractures which are not regarded as being associated with osteoporosis.[52] Exclusion of these cohorts from the analysis still

showed a similar pattern of association of lower leg fractures with BMI (data not shown). In the present study, a high BMI was a significant risk factor for humerus fractures and this persisted after adjustment for BMD. The finding is consistent with a recent short-term (1 year) prospective analysis in 832,775 Spanish women aged 50 years or more visiting general practitioners (SIDIAP),[16] in which a protective effect of obesity was found on future hip fracture and forearm fracture (relative risk [RR] = 0.49; 95% CI, 0.44–0.55, and RR = 0.83; 95% CI, 0.75–0.91, respectively), but obese women were at significantly higher risk of future proximal humeral fracture than the rest of the study population (RR = 1.28; 95% CI, 1.04–1.58). These findings are also consistent with an earlier report that obese women had a higher prevalence of a prior humeral fracture (odds ratio [OR] = 3.48; 95% CI, 0.18–6.68).[56] The reasons for the site-specific association between high BMI and humeral fracture risk are not known, though it may conceivably reflect a different pattern of falling or a greater load upon bones in the upper extremity in falls among the obese population. Moreover, a different padding effect of the soft tissues in different skeletal regions may produce diverse energy dissipation after trauma and, therefore, a different protection of the underlying bone.

Our results are at first sight at variance with the conclusions of Compston and colleagues,[15] who state that that obesity is not protective against fracture in postmenopausal women. That study, however, included a large number of non-adjudicated ankle and tibial fractures. Ankle fractures are not generally regarded as being associated with osteoporosis[51,56] and, as implied above, the accuracy of a self-reported distinction between ankle and other lower leg fractures is questionable. In their report, ankle fractures were significantly more frequent in obese compared with non-obese women. Given that the incidence of forearm, hip, pelvic, upper leg, and spine fractures was higher in underweight women than in obese women, their report is not inconsistent with our findings. Moreover, the present study also found a protective effect of low BMI for future lower leg fracture.

The question arises whether our findings have implications for the Fracture Risk Assessment Tool (FRAX®), which predicts the probability of a hip and a major fracture based on clinical risk factors such as sex, age, BMI, previous fracture, family history, glucocorticoid use, smoking, alcohol use, and secondary osteoporosis.[57] BMI is used as a continuous variable in FRAX, and BMD can be optionally entered into the model. Data from the meta-analysis of De Laet and colleagues[11] were used in the construct of FRAX. The association between BMI and the risk of hip fracture and other osteoporotic fractures in the present study is nearly identical to that described by De Laet and colleagues[11] in the absence of BMD. After adjustment for BMD, the risk of hip fracture associated with low BMI was attenuated in the same way as that described.[11] In the case of osteoporotic fractures, we have shown a slight though significant increase in risk with increasing BMI (see Table 6). This finding is consistent with the earlier meta-analysis, though the increase in risk was not statistically significant because of the smaller sample size. These considerations indicate that modifications of the FRAX algorithm are not warranted based on the present analysis; a view consistent with a recent report from the SOF study that FRAX is of value predicting fractures in obese women, particularly when used with BMD.[58]

The present study has several limitations, some of which we have discussed. These include the limited sampling frame for BMD measurements, inaccuracies in the estimate of BMD in the presence of a high fat mass, and uncertainties in the coding of some fractures. With regard to the first limitation, our results were similar when HRs not adjusted for BMD were calculated in those 27% of women in whom BMD was measured. The different settings of the cohorts are also a limitation, but that would weaken, not strengthen, an association between BMI and fracture. Conversely, the different settings increase the generalizability of our findings. The greatest limitation is that the present analysis is confined to women. Several lines of evidence suggest that the relationship between BMI and fracture risk may differ in men.[11,59]

A limitation in the understanding of possible mechanisms is that we have not been able to examine all potential confounding factors (eg, smoking, previous fracture, alcohol, comorbidities). Of possible relevance is the association of type 2 diabetes with high BMI. In a recent large clinical database in Manitoba, Canada, individuals with diabetes had a BMI approximately 3 kg/m^2 higher than those without diabetes.[60] Of particular interest, diabetes was associated with a 60% increased risk for major osteoporotic fracture when adjusted for clinical risk factors for fracture including BMI and BMD (HR = 1.61; 95% CI, 1.42–1.83). Thus, the higher risk for osteoporotic fracture for obese women (BMI 35 kg/m^2 versus 25 kg/m^2) in this report could be related in part to diabetes. Diabetic status was recorded in the present analysis for only 9% of women. In the women that had information on diabetes, the prevalence of diabetes was 3.4% in women with a normal BMI and 6.7% in obese women (data not shown). The small size of the available sample meant that we were unable to examine the impact of diabetes on the relationship between BMI and future fracture risk in more detail. The age interactions, the result with and without BMD and some of the fracture-specific findings might suggest an important role for low physical function and frailty in explaining these associations; but, as was the case for diabetes, we were unable to examine this further.

With these caveats, we conclude that low BMI remains an important clinical risk factor for hip and all osteoporotic fractures combined and that obesity in women is associated with a significant, albeit modest, reduction in fracture risk. In contrast, obese postmenopausal women appear to be at higher risk for humeral fractures than those with normal BMI. Moreover, after adjustment for BMD there is a slight increase in osteoporotic fracture risk with increasing BMI.

Disclosures

All authors state that they have no conflicts of interest.

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Original Full Length Article

Risk factors for falls in a longitudinal population-based cohort study of Japanese men and women: The ROAD Study

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ABSTRACT

The objective of this study was to clarify the associations of physical performance and bone and joint diseases with single and multiple falls in Japanese men and women using a population-based longitudinal cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD). A total of 452 men and 896 women were analyzed in the present study (mean age, 63.9 years). A questionnaire was used to assess the number of falls during the 3-year follow-up. Grip strength, 6-m walking time, and chair stand time were measured at baseline. Knee osteoarthritis (OA) and lumbar spondylosis were defined as Kellgren Lawrence = 2, 3 or 4. Vertebral fracture (VFx) was assessed with the Japanese Society of Bone and Mineral Research criteria. Osteoporosis was defined by bone mineral density using dual energy X-ray absorptiometry based on World Health Organization criteria. Knee and lower back pain were estimated by an interview. During a 3-year follow-up, 79 (17.4%) men and 216 (24.1%) women reported at least one fall, and 54 (11.9%) men and 111 (12.4%) women reported multiple falls. Knee pain was a risk factor for multiple falls in women, but not in men. VFx tended to be associated with multiple falls in women, but not in men. A longer 6-m walking time was a risk factor for multiple falls in women, whereas a longer chair stand time was a risk factor for multiple falls in men. We found gender differences in risk factors for falls.

Introduction

Falls are one of the main causes of injury, disability, and death among the elderly [1,2]. In Japan, according to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare, falls and fractures are ranked fifth among diseases that cause disabilities and subsequently require support with activities of daily living [3]. However, few population-based studies have been performed on the incidence of falls based on sex and age. Furthermore, in terms of factors associated with falls, muscle strength, balance, vision, functional capacities, and cognitive impairment are traits that diminish with aging, and these factors have been suggested as predictive risk factors for falls and fractures [4,5]. However, the association of bone and joint diseases, especially osteoarthritis (OA), with falls remains unclear.

The representative sites of OA are the knee and lumbar spine. Knee OA and lumbar spondylosis (LS) are major public health issues because they cause chronic pain and disability [6,7]. The prevalence rates of radiographic knee OA and LS are 54.6% and 70.2%, respectively, in persons aged 40 years and older in Japan, which indicates that 25,300,000 and 37,900,000 persons aged 40 years and older are estimated to experience radiographic knee OA and LS, respectively [10]. The National Livelihood Survey ranked OA fourth among diseases that cause disabilities and subsequently require support with activities of daily living [3], but there have been few studies of the association between falls and OA [11,12]. In previous studies, knee OA was assessed only by interview and not by radiography. The principal clinical symptom of knee OA is pain [13], but its correlation with the radiographic severity of knee OA is not as strong as expected [8]. In fact, in a study in Japan, approximately 20% of persons without knee OA had knee pain, and 30% of persons with severe knee OA had no knee pain [8]. Thus, knee OA diagnosed by interview could be limited by variable accuracy. In addition, men and women were not examined separately in these previous studies, although sex differences have been found in the prevalence of knee OA [8]. Our previous study showed that knee pain is significantly associated with falls in women [14], but that study used a cross-sectional design; thus, a causal relationship remains unclear. Regarding LS, to the best of our knowledge, no population-based studies have been performed

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regarding its association with falls except for our previous cross-sectional study [14], which showed that LS is not significantly associated with falls. In addition, among fractures due to osteoporosis (OP), vertebral fracture (VFx) is the most likely to lead to marked public health problems. VFx is reportedly associated with functional impairment [15], back pain, kyphosis [16,17], esophageal reflux [18], depressive mood [19], respiratory dysfunctions [20], and mortality [21]. However, whether VFx is an independent risk factor for the incidence of falls remains unclear.

Measuring walking speed is a simple way to assess health and function in older adults [22,23]. Walking speed has been found to be associated with falls in a few studies [4,24–26], although most studies were limited by a small sample size, a cross-sectional design [24,25], or evaluation of a single sex [4,26]. In addition, although walking abnormalities indicative by a slower walking speed are significantly associated with bone and joint diseases such as knee OA, LS, and their associated pain [14], no longitudinal studies have been performed to determine the associations of falls with bone and joint diseases and walking abnormalities at the same time. Furthermore, measuring the chair stand time is also reported to be a simple and established method to assess health and function in the elderly [27,28], but to the best of our knowledge, no longitudinal studies have been performed to determine the associations of falls with chair stand time.

Previous studies have shown that associations between individual risk factors and a single fall are few in number and weak compared to risk factors for multiple falls [12], indicating that single and multiple falls may have different backgrounds. Thus, to determine factors associated with falls, single and multiple falls should be analyzed separately.

The objective of this study was to clarify the associations of physical performance and bone and joint diseases with the incidence of single and multiple falls in Japanese men and women using a population-based longitudinal cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD).

Methods

Participants

The ROAD study is a nationwide, prospective study designed to establish epidemiologic indices for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (OP and OA are the representative bone and joint diseases, respectively). ROAD consists of population-based cohorts in three communities in Japan. A detailed profile of the ROAD study has been described elsewhere [8–10,29]; a brief summary is provided here. To date, we have completed the creation of a baseline database that includes clinical and genetic information for 3,040 participants (1,061 men and 1,979 women) ranging in age from 23 to 95 years (mean, 70.6 years) who were recruited from resident registration listings in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

Residents of these regions were recruited from the resident registration list of the relevant region. Participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database [30]. The participation rate was 75.6%. Participants in mountainous and coastal regions were also recruited from the resident registration lists, and the participation rates in these two areas were 56.7% and 31.7%, respectively. The inclusion criteria, apart from residence in the communities mentioned above, were the ability to (1) walk to the survey site, (2) report data, and (3) understand and sign an informed consent form. The baseline survey of the ROAD study was completed in 2006. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology.

Assessment of falls

Three years after the baseline data were obtained, we attempted to trace and review all 3,040 participants between 2008 and 2010; they were invited to attend a follow-up interview. All participants were interviewed with regard to falls by experienced interviewers and were asked the following questions: "Have you experienced falls during the 3-year follow-up, and if yes, how many falls did you experience"? At baseline, all participants were also interviewed regarding falls by experienced interviewers and were asked the following questions: "Have you experienced falls during the 12 months preceding baseline, and if yes, how many falls did you experience"? According to a previous study on falls [31], a fall is defined as a sudden, unintentional change in position causing an individual to land at a lower level on an object, the floor, or the ground, other than as a consequence of a sudden onset of paralysis, epileptic seizure, or overwhelming external force.

Pain assessment

All participants were interviewed by experienced orthopedists regarding knee pain and lower back pain at baseline and were asked the following questions based on previous studies [8,9]: "Have you experienced knee pain on most days in the past month, in addition to now"? and "Have you experienced lower back pain on most days in the past month, in addition to now"? Those who answered "yes" were defined as having pain. Buttock pain and sciatica were not included as lower back pain in the present study.

Radiographic assessment

At baseline, all participants underwent radiographic examination of both knees using anteroposterior and lateral views with weight-bearing and foot-map positioning; radiographic examination of the anteroposterior and lateral views of the lumbar spine, including intervertebral levels L1/2 to L5/S, was also performed. VFx was assessed by lateral radiographs of the lumbar spine (L1-L5) in terms of a wedge, biconcave, or crush appearance according to the Japanese Society of Bone and Mineral Research criteria [32]. The films were marked up, and morphometric measurements of anterior, middle, and posterior heights on lateral radiography of the thoracic and lumbar spine were made. Wedge appearance was defined as a site at which the anterior height of the vertebra was $\leq$75% of the posterior height. Biconcave appearance occurred if the height of the central part of the vertebra was $\leq$80% of that of the anterior or posterior parts of the vertebra. Crush appearance occurred if the height of the anterior, central, and posterior parts of an axial vertebra were all reduced to $\leq$80% of the normal value (Supplementary Fig. 1). Knee and lumbar spine radiographs were also read without knowledge of the participant's clinical status by a single, experienced orthopedist (S.M.) using the Kellgren Lawrence (KL) radiographic atlas [33] to determine the severity of KL grading. Radiographs were scored as grade 0–4, with higher grades associated with more severe OA. We defined knee OA and LS as KL $\geq$2 in at least one knee and one intervertebral level, respectively. To evaluate the intraobserver variability of KL grading, 100 randomly selected radiographs of the knee and lumbar spine were scored by the same observer more than 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopedic surgeons (S.M. and H.O.) using the same atlas for interobserver variability. The intra- and interobserver variabilities evaluated were confirmed by kappa analysis to be sufficient for assessment (0.86 and 0.80 for knee OA, and 0.84 and 0.76 for LS, respectively).

Bone mineral density (BMD) measurement

BMD was measured at the lumbar spine (L2–4) and the proximal femur using dual energy X-ray absorptiometry (DXA) (Hologic

Discovery; Hologic, Waltham, MA, USA) at baseline. For quality control, the same DXA equipment was used, and the same spine phantom was scanned daily to monitor the machine's performance in study populations at different regions. The BMD of the phantom was adjusted to 1.032 ± 0.016 g/cm^2 (±1.5%) during all examinations. In addition, the same physician (N.Y.) examined all participants to prevent observer variability. Coefficient of variance (CV) for L2–L4 in the phantom was 0.35%, and CVs for L2–L4, the proximal femur, Ward's triangle, and the trochanter examined in five volunteers were 0.61–0.90, 1.02–2.57, 1.97–5.45, and 1.77–4.17%, respectively [34].

OP was defined based on World Health Organization (WHO) criteria in which OP was diagnosed as T-scores of BMD ≤2.5 standard deviations (SDs) lower than peak bone mass [35]. Mean L2–4 BMD (SD) for young adult men and women measured using the Hologic QDR devices in Japan is reportedly 1.011 g/cm^2 (0.119 g/cm^2) [36]. Mean femoral neck BMD (SD) in Japan is reported to be 0.863 g/cm^2 (0.127 g/cm^2) for young men and 0.787 (0.109) for young women [36]. The present study therefore defined OP using these indices as lumbar spine BMD <0.714 g/cm^2 for both men and women, and as femoral neck BMD <0.546 g/cm^2 for men and <0.515 g/cm^2 for women.

Physical performance

At baseline, anthropometric measurements were taken, including height and weight, and body mass index (BMI) (weight [kg]/height^2 [m^2]) was estimated based on the measured height and weight. Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer (TOEI LIGHT CO., LTD, Saitama, Japan), and the best measurement was used to characterize maximum muscle strength. To measure physical performance, the time taken to walk 6 m at normal walking speed in a hallway was recorded. Participants were told to walk from a marked starting line to a 6-m mark as if they were walking down their hallway at home. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. The average of two trials was recorded. These gait-speed trial measurements are considered highly reliable in community-dwelling elderly persons [37]. The time taken for five consecutive chair rises without the use of hands was also recorded. Hands were folded in front of the chest with feet flat on the floor, following the protocol described by Guralnik et al. [27] and used by other researchers [28]. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. Timing began with the command "Go" and ended when the buttocks contacted the chair on the fifth landing. The reliability of this protocol is adequate [27].

Cognition assessment

At baseline, cognition was also evaluated for all participants using a Mini-Mental State Examination, and a cut-off score of <24 was used to select participants with cognitive impairment [38].

Statistical analyses

The differences in age and anthropometric measurements between the responders (those who completed the study) and non-responders (those lost to follow-up or who did not complete the study as described below) and between men and women were examined with a non-paired Student's *t*-test. Differences in physical performance measurements between the responders and non-responders and between men and women were examined with Wilcoxon signed-rank test. Differences in age and anthropometric measurements, among non-fallers, single fallers, and multiple fallers, were examined with one-way analysis of variance. Differences in physical performance measurements among non-fallers, single fallers, and multiple fallers were examined with the Kruskal–Wallis test. The prevalence of bone and joint diseases and cognitive impairment was compared between men and women and among non-fallers, single fallers, and multiple fallers with the chi square test. Multinomial logistic regression analysis after adjusting for age and BMI was used to determine the association of anthropometric measurements, physical performance, bone and joint diseases, and cognitive impairment with single and multiple falls compared with the absence of falls in men and women. Further, to determine an independent association of physical performance with single and multiple falls compared with the absence of falls, we used multinomial logistic regression analysis with age, BMI, 6-m walking time, and chair stand time as explanatory variables. To determine independent risk factors for single and multiple falls, we used multinomial logistic regression analysis with age, BMI, physical performance, bone and joint diseases, and cognitive impairment as explanatory variables. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 1,690 participants in the mountainous and seaside cohorts at baseline in 2006 and 2007, 40 (2.4%) had died by the time of the review 3 years later, 97 (5.7%) did not participate in the follow-up study due to poor health, 16 (0.9%) had moved away, 51 (3.0%) declined the invitation to attend the follow-up study, and 47 (2.8%) did not participate in the follow-up study for other reasons. Among the 1,439 volunteers who did participate in the follow-up study, 68 (4.0%) provided incomplete fall questionnaires. In addition, six (0.4%) provided incomplete pain questionnaires; these were excluded. We also excluded eight (0.5%) participants who had undergone total knee arthroplasty before baseline. An additional nine (1.9%) participants did not perform the 6-m walking time or chair stand time, leaving a total of 1,348 (79.8%) participants (452 men and 896 women) from whom radiographs at baseline and complete fall and pain histories were obtained. The mean followup time was 2.93 ± 0.12 years, ranging from 2.65 to 3.22 years. Table 1 shows characterisctics of responders and non-responders. The responders were significantly younger than the non-responders (63.9 and 70.7 years, respectively). Physical performance measurements were better in responders than non-responders. Prevalence of knee OA, LS and knee pain was lower in responders (47.0, 61.6 and 9.7%,

Table 1
Baseline characteristics of responders and non-responders.

	Overall	Responders	Non-responders
Number of participants	1,690	1,348	342
Female (%)	64.7	66.5	57.9***
Age (years)	65.2 ± 12.0	63.9 ± 11.8	70.7 ± 11.4*
Height (cm)	155.2 ± 9.3	155.6 ± 9.0	153.6 ± 10.1*
Weight (kg)	55.6 ± 10.8	56.1 ± 10.7	53.7 ± 10.8*
BMI (kg/m^2)	23.0 ± 3.4	23.1 ± 3.4	22.7 ± 3.4
Grip strength (kg) (median [IQR])	26.0 [21.0–33.0]	26.0 [21.0–34.0]	24.0 [18.0–30.0]**
6-m walking time (s) (median [IQR])	5.0 [4.0–7.0]	5.0 [4.0–6.0]	7.0 [5.0–9.0]**
Chair stand time (s) (median [IQR])	9.0 [7.0–12.0]	9.0 [7.0–11.0]	12.0 [8.25–15.0]**
Cognitive impairment (%)	4.5	2.8	11.4***
Radiographic knee OA (%)	50.4	47.0	63.8***
Radiographic LS (%)	63.2	61.6	69.1***
Radiographic VFx	10.1	9.7	12.0
Knee pain (%)	24.3	22.2	32.6***
Lower back pain (%)	21.1	20.6	22.9
Previous falls (%)	17.3	16.3	21.0***

Values are mean ± SD, except where indicated.
BMI: body mass index, OA: osteoarthritis, LS: lumbar spondylosis, VFx: vertebral fracture, IQR: interquartile range.
* $p<0.05$ vs. responders by non-paired Student's *t*-test.
** $p<0.05$ vs. men by Wilcoxon signed-rank test.
*** $p<0.05$ vs. men by chi square test.

Table 2
Baseline characteristics of participants.

	Men	Women
Number of participants	452	896
Age (years)	64.9 ± 11.7	63.3 ± 11.8*
Height (cm)	164.0 ± 7.0	151.3 ± 6.6*
Weight (kg)	63.3 ± 10.7	52.5 ± 8.7*
BMI (kg/m^2)	23.5 ± 3.2	22.9 ± 3.4*
Grip strength (kg) (median [IQR])	37.0 [32.0–42.5]	23.5 [20.0–23.5]**
6-m walking time (s) (median [IQR])	5.0 [4.0–6.0]	5.0 [4.0–6.0]
Chair stand time (s) (median [IQR])	8.5 [7.0–11.0]	9.0 [7.0–11.0]
Cognitive impairment (%)	3.6	2.4
Radiographic knee OA (%)	37.4	51.9***
Radiographic LS (%)	76.1	54.2
Radiographic VFx	8.9	10.1
Knee pain (%)	15.3	25.7***
Lower back pain (%)	18.8	21.5
Previous falls (%)	13.1	18.0***

Values are mean ± SD, except where indicated.
BMI: body mass index, OA: osteoarthritis, LS: lumbar spondylosis, VFx: vertebral fracture, IQR: interquartile range.
* $p<0.05$ vs. men by non-paired Student's *t*-test.
** $p<0.05$ vs. men by Wilcoxon signed-rank test.
*** $p<0.05$ vs. men by chi square test.

respectively) than non-responders (63.8, 69.1 and 12.0, respectively). Prevalence of previous falls was significantly lower in responders than non-responders (16.3 and 21.0%, respectively).

Table 2 shows the age, anthropometric measurements, physical performance, and prevalence of cognitive impairment, bone and joint diseases, and previous falls of participants at baseline in men and women. Regarding physical performance, grip strength and chair stand time were significantly better in men (37.0 kg and 8.5 s, respectively) than in women (23.5 kg and 9.0 s, respectively), but the 6-m walking time was not (5.0 s and 5.0 s, respectively). The prevalence of radiographic knee OA and knee pain was significantly higher in women (51.9% and 25.7%, respectively) than in men (37.4% and 15.3%, respectively), whereas that of LS and lower back pain was not different between men and women. The prevalence of previous falls was significantly higher in women than in men (18.0% and 13.1%, respectively).

During the 3-year follow-up, 79 (17.4% [95% confidence interval [CI] 14.3–21.2]) men and 216 (24.1% [95% CI 21.4–27.0]) women reported at least one fall, and 54 (11.9% [95% CI 9.3–15.3]) men and 111 (12.4% [95% CI 10.4–14.7]) women reported multiple falls. The chi square test showed that the incidence of falls was significantly different between men and women ($p=0.0011$). The incidence of single and multiple falls was significantly higher in the mountainous regions (11.5% and 17.4%, respectively) than coastal regions (8.1% and 7.8%, respectively). With increasing age, the incidence of falls increased in women, but the incidence of falls was similar in men in their 60s and 70s (Fig. 1).

Table 3 shows the age, anthropometric measurements, physical performance, and BMD at baseline between non-fallers, single fallers, and multiple fallers. Age and BMI were significantly higher in female fallers than non-fallers, but this was not the case in men. Grip strength was worse in female fallers than non-fallers, but this was not the case in men. The 6-m walking time and chair stand time were longer in both male and female fallers than in non-fallers. LS and neck BMD were significantly lower in female fallers than non-fallers, but this was not the case in men.

We next examined the incidence rate of falls during the 3-year follow-up according to previous falls at baseline in men and women (Supplementary Fig. 2). The incidence rates of multiple falls were 7.9%, 22.7%, and 48.7% in men and 8.8%, 20.4%, and 43.1% in women among non-fallers, single fallers, and multiple fallers, respectively. The incidence rates of single falls were 5.9%, 9.1%, and 0.0% in men and 12.5%, 7.8%, and 8.6% in women among non-fallers, single fallers, and multiple fallers, respectively. The chi square test showed that the incidence of falls during the 3-year follow-up was significantly associated with previous falls at baseline in men and women ($p<0.0001$).

Fig. 2 shows the incidence rate of falls during the 3-year follow-up according to the presence of bone and joint diseases and cognitive impairment. The incidence rates of multiple falls were 16.6% and 9.2% in men and 14.8% and 9.7% in women in those with and without knee OA, respectively. The incidence rates of a single fall were 8.3% and 3.9% in men and 14.2% and 9.1% in women in those with and without knee OA, respectively. The chi square test showed that knee OA at baseline was significantly associated with the incidence rate of falls during the 3-year follow-up in men and women ($p<0.0001$). Regarding knee pain, the incidence rates of multiple falls were 18.8% and 10.7% in men and 18.7% and 10.2% in women in those with and without knee pain, respectively. The incidence rates of a single fall were 8.7% and 5.0% in men and 10.4% and 10.4% in women in those with and without knee OA, respectively. The chi square test showed that knee pain at baseline was significantly associated with the incidence of falls during the 3-year follow-up in men and women ($p<0.0001$). LS and lower back pain were not significantly associated with the incidence of falls in men ($p=0.52$ and 0.77, respectively) or in women ($p=0.45$ and 0.58, respectively). VFx at baseline was significantly associated with the incidence of falls in women (multiple falls 22.2% and 11.3%, single falls 14.4% and 11.4%, in those with and without VFx, respectively, $p=0.005$), but not in men ($p=0.06$). OP defined by L2–4 and femoral neck BMD was not associated with the incidence of falls in men and women. Cognitive impairment

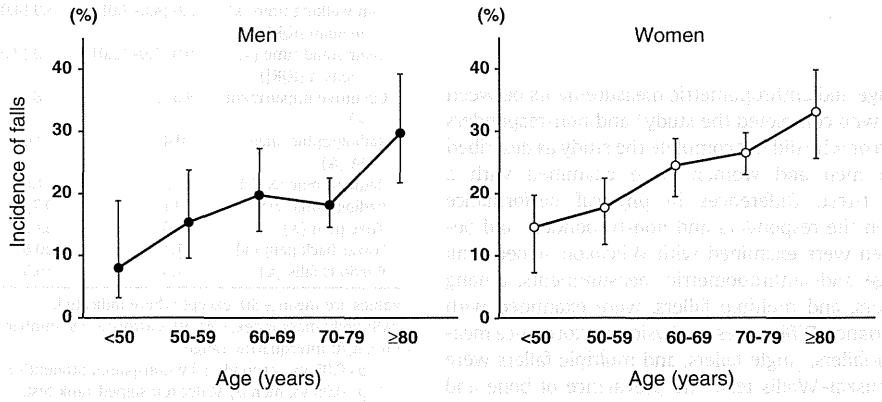

Fig. 1. Incidence rate of falls (error bars represent 95% confidence intervals) by gender and age strata.

Table 3
Comparison of characteristics among non-fallers, single fallers, and multiple fallers in men and women.

	Men				Women			
	Non-fallers	Single fallers	Multiple fallers	p value	Non-fallers	Single fallers	Multiple fallers	p value
Number of participants	373	25	54		680	105	111	
Age (years)	64.4 (11.7)	67.2 (13.2)	67.6 (10.1)	0.10	62.4 (11.6)	66.0 (12.6)	66.7 (11.4)	<0.001
BMI (kg/m^2)	23.4 (3.1)	24.6 (3.9)	23.7 (3.3)	0.16	22.8 (3.5)	22.7 (3.1)	23.8 (3.5)	0.01
Grip strength (kg) (median [IQR])	37.0 [32.0–43.0]	37.0 [30.0–41.5]	35.0 [28.8–40.0]	0.08	24.0 [20.0–27.0]	23.0 [19.5–27.0]	22.0 [18.0–26.0]	0.01
6-m walking time (s) (median [IQR])	4.5 [4.0–6.0]	5.5 [4.6–7.3]	6.2 [5.0–6.6]	<0.0001	5.0 [4.0–6.0]	5.0 [4.0–6.5]	5.5 [4.0–7.5]	<0.0001
Chair stand time (s) (median [IQR])	8.0 [7.0-10.0])	11.0 [9.0-12.0]	10.0 [8.0-13.0]	<0.0001	9.0 [7.0-11.0]	9.0 [8.0-12.0]	10.0 [8.0-12.25]	0.0001
LS BMD	1.05 (0.20)	1.05 (0.20)	1.05 (0.15)	0.99	0.89 (0.18)	0.85 (0.16)	0.86 (0.17)	0.04
Neck BMD	0.75 (0.13)	0.77 (0.12)	0.75 (0.10)	0.79	0.65 (0.13)	0.61 (0.11)	0.63 (0.11)	0.003

Values are the means (standard deviation), except where indicated.
One-way analysis of variance was used to determine the differences in age, height, weight and BMI among non-fallers, single fallers, and multiple fallers.
Kruskal–Wallis test was used to determine the differences in grip strength, 6-m walking time and chair stand time among non-fallers, single fallers, and multiple fallers.
The chi square test was used to determine the differences in the prevalence of cognitive impairment among non-fallers, single fallers, and multiple fallers.
BMI: body mass index, LS: lumbar spondylosis, BMD: bone mineral density.

was associated with the incidence of falls in men (multiple falls 31.3% and 10.9%, single falls 18.8% and 5.1%, in those with and without cognitive impairment, respectively, $p=0.002$), but not in women ($p=0.19$).

In men, multinomial logistic regression analysis after adjusting for age and BMI showed that a longer 6-m walking time, longer chair stand time, and previous falls were risk factors for falls, but grip strength, bone and joint diseases, and cognitive impairment were not

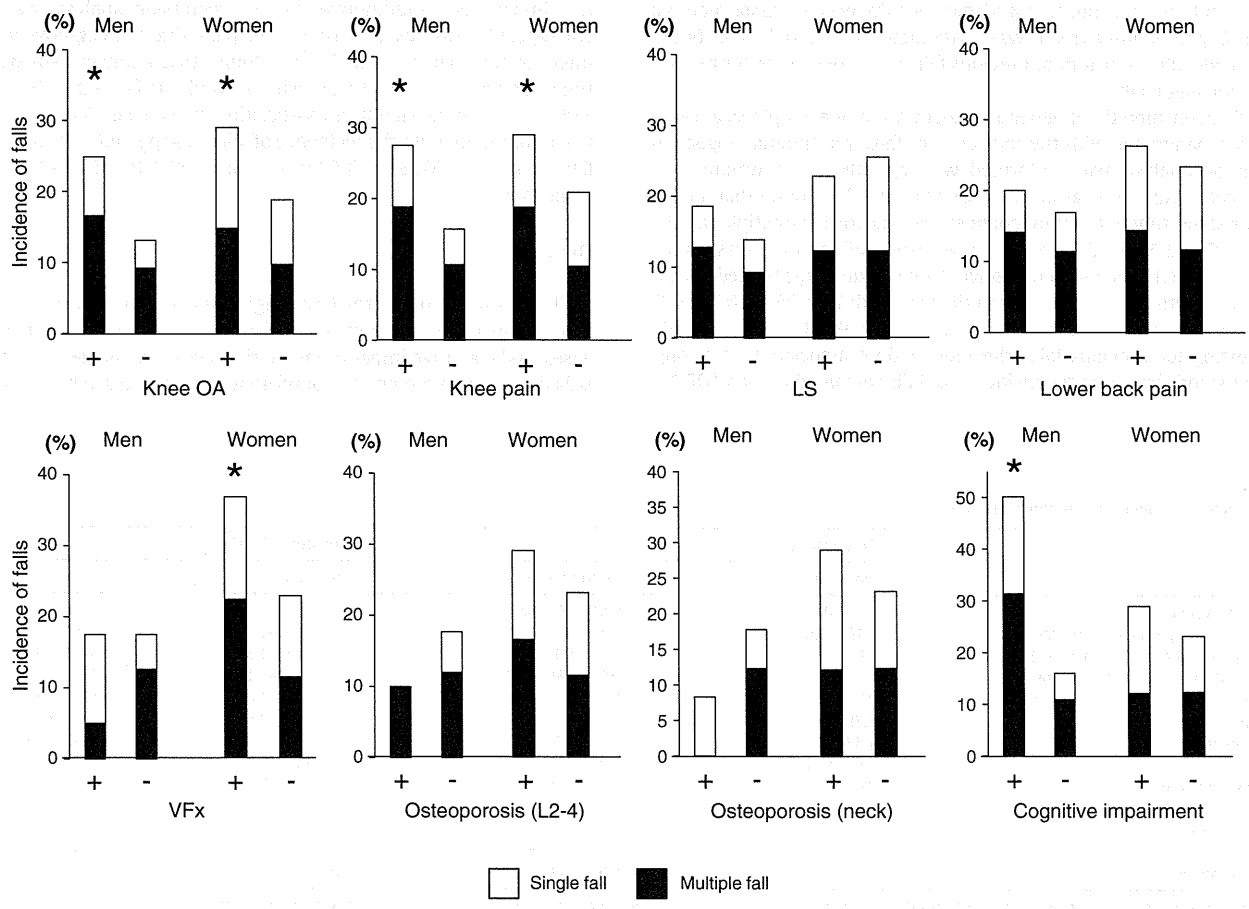

Fig. 2. Incidence of single and multiple falls by bone and joint diseases and cognitive impairment. *$p<0.05$ vs. participants without each disease or pain, respectively, according to the chi square test. OA, osteoarthritis; LS, lumbar spondylosis; VFx, vertebral fracture.

Table 4
Risk factors for single and multiple falls in men.

	Crude OR (95% CI)		Adjusted OR (95% CI)	
	Single falls	Multiple falls	Single falls	Multiple falls
Grip strength (5 kg increase)	0.90 (0.71–1.14)	0.84 (0.71–0.99)	1.14 (1.01–1.29)	0.88 (0.72–1.08)
6-m walking time (1 s increase)	1.12 (0.98–1.27)	1.13 (1.03–1.26)	1.11 (0.95–1.25)	1.11 (1.01–1.23)
Chair stand time (1 s increase)	1.17 (1.03–1.32)	1.21 (1.11–1.33)	1.15 (1.00–1.32)	1.21 (1.09–1.33)
LS BMD (0.1 mg/cm^2 increase)	1.00 (0.80–1.22)	1.00 (0.86–1.16)	0.92 (0.73–1.15)	0.97 (0.83–1.13)
Neck BMD (0.1 mg/cm^2 increase)	1.10 (0.81–1.47)	0.98 (0.78–1.21)	1.07 (0.73–1.51)	1.01 (0.77–1.30)
Knee OA	2.44 (1.09–5.56)	2.08 (1.18–3.70)	2.07 (0.84–5.21)	1.77 (0.95–3.33)
Knee pain	2.04 (0.72–5.09)	2.05 (0.99–4.00)	1.65 (0.57–4.21)	1.78 (0.85–3.55)
VFx	2.58 (0.82–6.85)	0.40 (0.06–1.36)	2.48 (0.75–7.04)	0.32 (0.05–1.13)
Cognitive impairment	6.19 (1.29–23.1)	4.83 (1.41–15.1)	13.48 (0.98–178.64)	3.17 (0.44–21.99)
Previous falls				
Single fall	–	–	–	3.52 (1.07–9.97)
Multiple falls	1.18 (0.25–4.61)	9.54 (3.15–30.08)	–	12.6 (5.80–27.97)

Multinomial logistic regression analysis was used to calculate the crude odds ratio (OR) and 95% confidence interval (CI) compared with non-fallers.
Adjusted OR was calculated using multinomial logistic regression analysis after adjusting for age and body mass index (BMI).
OA: osteoarthritis, VFx: vertebral fracture, BMD: bone mineral density, LS: lumbar spondylosis.
Radiographic knee OA was defined as Kellgren Lawrence grade 3 or 4.

(Table 4). Previous falls were significantly associated with the incidence of multiple falls. In women, multinomial logistic regression analysis after adjusting for age and BMI showed that a longer 6-m walking time was a risk factor for multiple, but not single falls (Table 5). Chair stand time also tended to be associated with the incidence of single and multiple falls. Regarding bone and joint diseases, knee pain was a risk factor for single and multiple falls. VFx also tended to be associated with multiple falls, but radiographic knee OA was not associated with falls. Cognitive impairment was a risk factor for multiple falls, but not for single falls. A history of previous falls was a risk factor for multiple, but not single falls.

To determine the independent association of each physical performance parameter with the incidence of falls, multinomial logistic regression analysis was performed with age, BMI, 6-m walking time, and chair stand time as explanatory variables. We found that a longer chair stand time was an independent risk factor for multiple falls (OR 1.18, 95% CI 1.06–1.32), but a longer 6-m walking time was not (OR 1.05, 0.93–1.16). In women, a longer 6-m walking time tended to be associated with the incidence of multiple falls (OR 1.09, 95% CI 0.98–1.22), but a longer chair stand time was not (OR 1.01, 95% CI 0.94–1.07). After adjusting for previous falls, the independent association of a longer chair stand time with the incidence of falls remained in men (OR 1.15, 95% CI 1.02–1.30), and the independent association of a longer 6-m walking time with the incidence of falls remained in women (OR 1.12, 95% CI 1.00–1.25). In addition, knee pain and cognitive impairment in women were also significantly associated with falls, and VFx tended to be associated with falls with multinomial logistic regression analysis after adjusting for age and BMI. Thus, to determine the independent association of physical performance, bone and joint diseases, and cognitive impairment, multinomial logistic regression analysis was used with age, BMI, 6-m walking time, knee pain, VFx, and cognitive impairment as explanatory variables. We found that a longer 6-m walking time was an independent risk factor for multiple falls (OR 1.08, 95% CI 1.00–1.18), but the significant association of knee pain, VFx, and cognitive impairment with the incidence of falls disappeared (OR 1.47, 95% CI 0.91–2.35, OR 1.52, 95% CI 0.80–2.81, and OR 1.16, 95% CI 0.35–3.24, respectively).

Discussion

The present study is the first longitudinal population-based cohort study to examine whether physical performance, bone and joint diseases, and cognitive impairment are risk factors for single and multiple falls in men and women. We found gender differences in risk factors for

Table 5
Risk factors for single and multiple falls in women.

	Crude OR (95% CI)		Adjusted OR (95% CI)	
	Single falls	Multiple falls	Single falls	Multiple falls
Grip strength (5 kg increase)	0.84 (0.70–0.99)	0.81 (0.68–0.95)	0.94 (0.77–1.11)	0.91 (0.75–1.08)
6-m walking time (1 s increase)	1.10 (1.01–1.19)	1.16 (1.08–1.25)	1.04 (0.94–1.14)	1.11 (1.02–1.20)
Chair stand time (1 s increase)	1.07 (1.02–1.12)	1.07 (1.03–1.12)	1.04 (0.99–1.10)	1.04 (0.99–1.09)
LS BMD (0.1 mg/cm^2 increase)	0.88 (0.78–1.00)	0.90 (0.80–1.01)	0.96 (0.83–1.11)	0.92 (0.80–1.06)
Neck BMD (0.1 mg/cm^2 increase)	0.75 (0.63–0.90)	0.85 (0.72–1.01)	0.79 (0.62–1.01)	0.87 (0.69–1.10)
Knee OA	1.79 (1.18–2.78)	1.75 (1.16–2.63)	1.52 (0.94–2.50)	1.12 (0.79–1.82)
Knee pain	1.83 (1.17–2.83)	2.22 (1.44–3.37)	1.62 (1.00–2.60)	1.60 (1.00–2.54)
VFx	1.54 (0.78–2.85)	2.40 (1.35–4.12)	1.15 (0.57–2.20)	1.81 (0.98–3.24)
Cognitive impairment	0.42 (0.02–2.12)	2.12 (0.68–5.60)	0.73 (0.19–2.61)	4.95 (1.50–16.08)
Previous falls				
Single fall	0.55 (0.16–1.74)	1.51 (0.33–5.41)	0.70 (0.30–1.43)	2.48 (1.40–4.28)
Multiple falls	0.86 (0.39–1.81)	8.55 (3.80–19.20)	1.06 (0.35–2.62)	6.93 (3.76–12.72)

Multinomial logistic regression analysis was used to calculate the crude odds ratio (OR) and 95% confidence interval (CI) compared with non-fallers.
Adjusted OR was calculated using multinomial logistic regression analysis after adjusting for age and body mass index (BMI).
OA: osteoarthritis, VFx: vertebral fracture, BMD: bone mineral density, LS: lumbar spondylosis.
Radiographic knee OA was defined as Kellgren Lawrence grade 3 or 4.

falls. Regarding physical performance, a longer chair stand time was an independent risk factor for falls in men, whereas a longer 6-m walking time was an independent risk factor for falls in women. Knee pain, VFx, and cognitive impairment were associated with falls in women, but not in men.

The present study is a population-based longitudinal study to determine whether bone and joint diseases are risk factors for falls in Japanese men and women. After adjusting for age and BMI, knee pain was a risk factor for falls in women, but not in men. The sex differences regarding the association of knee pain with falls may be partly explained by the weaker quadriceps muscles in women, which is known to be an independent risk factor for falls [16]. Muscle strength is higher in men than in women in all decades [39], which may obscure the association of knee pain with falls. In addition, given the insignificant association of radiographic knee OA with falls, falls may occur due to symptoms such as pain rather than radiographic changes in the knee itself. Our study and other previous cross-sectional studies also suggested that knee pain is significantly associated with falls [11]. In other words, falls may be preventable when pain is relieved by medical care, even if patients have radiographic knee OA.

In the present study, LS and lower back pain were not associated with falls, whereas VFx was associated with falls. Lower BMD was not associated with falls in the present study, and thus, radiographic changes but not OP may be associated with falls. Studies of patients with VFx have reported increased kyphosis angles [16,17], which is an independent risk factor for injurious falls [40]. Previous studies [41,42] have demonstrated that people with kyphosis have greater balance abnormalities as assessed by computerized dynamic posturography. Specifically, they reported that women with OP-related kyphosis had greater mediolateral displacement and increased mediolateral velocity compared to controls [42]. In addition, lateral spontaneous sway amplitude has been reported to be the single best predictor of future risk of falls [43]. These observations may partly explain the association between VFx and falls.

In the present study, after adjusting for age and BMI, both a longer 6-m walking time and a longer chair stand time were associated with falls in men and women. A previous study also showed that slower walking speed is a risk factor for falls [44], although men and women were not separately analyzed in the study. To determine the independent association of the 6-m walking time and chair stand time, we further used multinomial logistic regression analysis with age, BMI, 6-m walking time, and chair stand time as explanatory factors, and found that in men, a longer chair stand time was an independent risk factor for multiple falls, but a longer 6-m walking time was not. In women, a longer 6-m walking time was associated with the incidence of multiple falls, whereas a longer chair stand time was not. This indicates that slower walking speed may more strongly affect the risk of falling in women than in men, whereas a longer chair stand time may more strongly affect the risk of falling in men than in women. The walking time and chair stand time can be easily and quickly measured in clinical and research settings without requiring monitoring devices or extensive training. The present study may indicate that walking time is a simple and quick option for measuring the risk of falling, particularly in women, and measuring the chair stand time is a simple and quick option for estimating the risk of falling, particularly in men.

The present study has several limitations. First, our participants lived in the community, and thus, our findings may not apply to elderly persons residing in institutions. Second, we did not include other anatomical locations of weight-bearing OA such as hip OA in the analysis, although this disorder also affects falls [45]. However, the prevalence of KL=3 or 4 hip OA is 1.4% and 3.5% in Japanese men and women [46], respectively, which is lower than that of KL=3 or 4 knee OA (12.2% and 21.0% in men and women, respectively) in the present study. Thus, it is possible that hip OA would not strongly affect the results of the present study. Third, non-responders were older, had lower physical performance and higher prevalence of knee pain, which were risk factors for falls. This means that the incidence of falls in the present study may have been underestimated. Fourth, the accuracy and reliability of recall of falls over the past 3 years was not assessed in the present study. Previous studies have shown that 13–32% of elderly subjects with confirmed falls did not recall falling over a 12-month period [47], even when excluding subjects with cognitive impairment. Therefore, the incidence of falls may be underestimated, particularly in older subjects and those with cognitive impairment. In addition, individuals are more likely to recall a fall that resulted in injury, which may have influenced the results of this study.

Conclusion

The present longitudinal analysis using a large-scale population from the ROAD study revealed gender differences in risk factors for falls. A longer walking time was a risk factor for falls in women, whereas a longer chair stand time was a risk factor for falls in men. Knee pain and VFx were risk factors for falls in women, but not in men. Further studies, along with continued longitudinal surveys in the ROAD study, will help elucidate the background of bone and joint diseases and their relationship with falls.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.bone.2012.10.020.

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ORIGINAL ARTICLE

Skipping breakfast and less exercise are risk factors for bone loss in young Japanese adults: a 3-year follow-up study

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Abstract Although bone loss contributes to osteoporosis (OP) in the elderly, little is known about changes in bone mineral density (BMD) in young adults that lead to bone loss. Here, we evaluated the rate of bone change and risk factors for bone loss in young men and women using data from a 3-year prospective study of Japanese medical students. The study included a self-administrated questionnaire survey, anthropometric measurements, and BMD measurements of the spine (L2–L4) and femoral neck (FN). After 3 years, the BMD of the participants was again measured at the same sites. In all, 458 students (95.4 %; 298 men and 160 women; age range, 18–29 years; mean age, 20.2 years) completed both the baseline and follow-up surveys. The mean L2–L4 BMD value at baseline increased significantly within 3 years. This tendency was also observed for the FN in men but not in women. The annual changes at L2–L4 were 1.78 % in men and 0.97 % in women per year; those for FN were 1.08 % in men and 0.08 % in women per year. However, 20.3 % and 38.5 % of the total freshmen lost BMD in the lumbar spine and FN, respectively. After adjustment for age and body mass index, logistic regression analysis revealed that bone loss in men at L2–L4 at the baseline was affected by skipping breakfast. In contrast, exercise (>2 h/week) increased lumbar spine BMD in both genders. These findings indicate that breakfast and exercise are important for maintaining BMD in young men and women.

Keywords Bone loss · Breakfast · Exercise · Young adults · Prospective study

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Introduction

Bone loss is one of the key determinants of osteoporosis (OP), which is widely recognized as a serious public health problem because of its significantly high morbidity with or without fractures [1, 2]. Studies on bone loss have reported age-related distributions of changes in bone mineral density (BMD) in middle-aged and elderly residents in mountainous [3, 4] and seaside villages [5] in Japan, using data from longitudinal observations of these populations. However, few studies to date have reported changes in BMD in young adults, particularly in their twenties, despite the fact that peak bone mass (PBM) is achieved in adolescence.

PBM, another key determinant of skeletal health throughout life, increases substantially during the first 20 years before reaching a plateau in both men and women; however, the timing of this plateau is still controversial. Some studies have reported PBM as early as 20 years of age [6, 7]. Baxter-Jones et al. [8] reported that PBM in their cohort of male and female adolescents occurred by the end of the second decade or very early in the third decade. In a previous study, we reported that the PBM at the femoral neck (FN) site in young Japanese men might occur before 20 years and then decrease [9]; however, we could not determine the change in BMD because of the cross-sectional design of the study. Here, we used

the follow-up data of young medical students to clarify bone changes in young men and women. In addition, factors that might influence changes in BMD at young ages to prevent OP and osteoporotic fractures in middle-aged men and women, specifically diet and exercise, were evaluated in young men and women.

Materials and methods

Participants

All 480 freshmen enrolled in Wakayama Medical University from 1993 to 2000 were recruited in this study, with an average of 60 freshmen every year for 8 years. All participants provided written informed consent in advance of their participation in the study. Among these 480 students, 463 (96.5 %) completed both the initial baseline and the subsequent follow-up survey 3 years later. Among the 463 participants, 5 participants were excluded because they were older than 30 years. Data from the remaining 458 participants were analyzed (95.4 %; 298 men and 160 women; age range, 18–29 years; mean age, 20.2 years).

Questionnaire survey regarding lifestyle factors

All participants completed a self-administered questionnaire consisting of 70 items covering medical history, including past fractures, injury, diabetes mellitus, renal diseases, gastric diseases, and back pain. The survey also covered medication information, including use of steroid hormones, oral contraceptive pills, minor tranquilizers, and calcium supplementation. In addition, the survey contained questions regarding family history of bone fractures, OP, back pain, alcohol consumption, and smoking status. The survey also covered physical performance, including whether participants could stand on the trains or buses, sit down in a chair, sit up with their heels, be active on holidays, sleep on a futon (Japanese-style mattress); sleeping time; toilet style; nutritional habits; and exercise time in regular sports. For female students, questions regarding the age of menarche and whether their periods were regular or irregular were also included.

Nutrition and exercise habits were also assessed. The frequency of consumption (every day, 3–4 times a week, 1–2 times a week, 1–2 times a month, or less than once a month) was recorded for food categories such as meat, fish, vegetables, fruits, snacks, beverages, and dairy products. Milk intake frequency (every meal, every day, every week, or less than once per week) was recorded for elementary school, junior high school, high school, and the present. In addition, breakfast consumption frequency (every day, sometimes, or skipping) was recorded for elementary school, junior high school, high school, and the present. Exercise duration per week ($\geq$10 h per week, 5–10 h per week, 2–5 h per week, 1–2 h per week, or <1 h per week) and types of regular sports (walking, gymnastics, golf, cycling, jogging, swimming, and other activities specified) were also recorded for elementary school, junior high school, high school, and the present.

BMD and anthropometric measurements

BMD was measured using dual-energy X-ray absorptiometry (DXA) (Lunar DPX-1000; GE Lunar, Madison, WI, USA) from anteroposterior images at the lumbar spine L2–L4 and proximal femur (FN, Ward's triangle, and trochanter) sites. In addition to BMD measurements, physical parameters such as height, weight, arm span, dominant wrist circumference, and grip strength were measured, and body mass index (BMI, kg/m^2) was calculated.

To control precision of the DXA apparatus, the equipment was checked at every examination using the same phantom, with BMD of the phantom regulated to 1.270 $\pm$ 0.025 g/cm^2 (2 %). In addition, all participants were examined by the same medical doctor (N.Y.) to control observer variability. Intraobserver variability of DXA in vitro and in vivo has been measured in a prior study by the same medical doctor. Coefficient of variation (CV %) for L2–L4 in vitro was determined to be 0.35 %, whereas CV % for L2–L4, FN, Ward's triangle, and trochanter examined in vivo in five male volunteers was 0.61–0.90 %, 1.02–2.57 %, 1.97–5.45 %, and 1.77–4.17 %, respectively [10].

Three-year follow-up

As a follow-up survey 3 years later when the students were in their fourth year of medical school, their BMD was measured again at the same sites previously measured at baseline, and questionnaires regarding changes of lifestyle were reexamined by the same investigator (N.Y.).

Statistical analysis

All statistical analyses were performed using JMP version 8 (SAS Institute Japan, Tokyo, Japan) and STATA version 10 (STATA, College Station, TX, USA). Differences in age and anthropometric measures such as height, weight, BMI, grip strength, BMD values, and age of menarche were examined using an unpaired Student's t test. Categorical variables, such as smoking status, alcohol intake, coffee intake, skipping breakfast, milk intake, exercise, past history of fractures at any sites, family history of OP, and diet history, were examined using the chi-squared test. Finally, logistic regression analysis, with occurrence of